AD_____

Award Number: DAMD17-02-1-0358

TITLE: Monitoring Cancer Oxygenation Changes Induced by Ultrasound

PRINCIPAL INVESTIGATOR: Anastasios Maurudis, Ph.D.
Quing Zhu, Ph.D.

CONTRACTING ORGANIZATION: University of Colorado
Storrs, CT 06269-4133

REPORT DATE: July 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-07-2005	Annual Summary	15 Jun 2004 – 14 Jun 2005

4. TITLE AND SUBTITLE
Monitoring Cancer Oxygenation Changes Induced by Ultrasound

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-1-0358

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Anastasios Maurudis, Ph.D.
Quing Zhu, Ph.D.

E-mail: MAURUDIS@IEEE.ORG

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Colorado
Storrs, CT 06269-4133

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Preliminary studies with 5 tumor-bearing rats performed by the original PI, Dr. Daqing Piao, demonstrated that ultrasonic vibrations could either generate significant effects (early stage tumors) on optical measurements or no effects on optical measurements (late stage tumors). During the first two years, the original PI had devoted his efforts on quantifying both acoustic vibration and optical measurement of oxygenation. He had completed the first two proposed tasks and partially competed the third task. The original PI finished his Ph.D training at UConn and accepted a Post Doc position at Dartmouth College at end of July 2004. I was appointed by Prof. Zhu (Mentor of the training grant) to continue this training grant on Sept 2004. My appointment was approved by the D.O.D. around May 2005. I was given a one-year extension to complete this project. Since May 2005, I have been studying the relevant literature and also linking my photo-acoustic small animal research project funded by NIH with this training grant.

15. SUBJECT TERMS
Cancer therapy, cancer hypoxia, optical spectroscopy, ultrasound agent

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	6	

Table of Contents

Introduction:

Annually, more than 200,000 American women are diagnosed with breast cancer and nearly 40,000 die from the disease. It is the second leading cause of death among American women. The treatment of breast cancer includes surgery, radiation, chemotherapy, and hormonal modification. Despite the development of new techniques to characterize the biologic features of breast tumors, the factors influencing the quality of response to therapy remain obscure. Biological makers have shown an ability to predict breast cancer response to only particular forms of therapy [1-2]. One factor that may influence response to systemic chemotherapy is tumor perfusion [3-4]. Tumors with relatively poor perfusion may receive inadequate delivery of systemic therapy. This lack of blood flow to the tumor may be a factor in poor response to intravenous chemotherapy [5]. Furthermore, underperfused tumors may be hypoxic [6-7]. Hypoxia has been implicated in the induction of biologic features associated with aggressive behavior and poor response to various forms of chemotherapy [4]. A recent publication in Nature Medicine using the angiogenesis inhibitor bevacizumab in patients with rectal cancer, has shown this therapy to be associated with improved oxygenation and reduced blood vessel permeability within the tumor [8]. This may result in improved delivery of chemotherapy to the tumor and reduction in metastatic potential.

Body:

Our hypothesis was

a) Tumor blood vessels were leaky and therefore acoustic vibration can be used to modulate the leaky vessels and induce oxygenation changes and improve tumor oxygenation.
b) The oxygenation changes can be detected by optical measurements.

Preliminary studies with 5 tumor-bearing rats performed by the original PI, Dr. Daqing Piao, demonstrated that ultrasonic vibrations could either generate significant effects (early stage tumors) on optical measurements or no effects on optical measurements (late stage tumors).

During the first two years, the original PI had devoted his efforts on quantifying both acoustic vibration and optical measurement of oxygenation. He had completed the first two proposed tasks and partially competed the third task. The original PI finished his Ph.D training at UConn and accepted a Post Doc position at Dartmouth College at end of July 2004. I was appointed by Prof. Zhu (Mentor of the training grant) to continue this training grant on Sept 2004. My appointment was approved by the Department of Defense around May 2005. I was given a one-year extension to complete this project. Since May 2005, I have been studying the relevant literature and also linking my photo-acoustic small animal research project funded by NIH with this training grant.

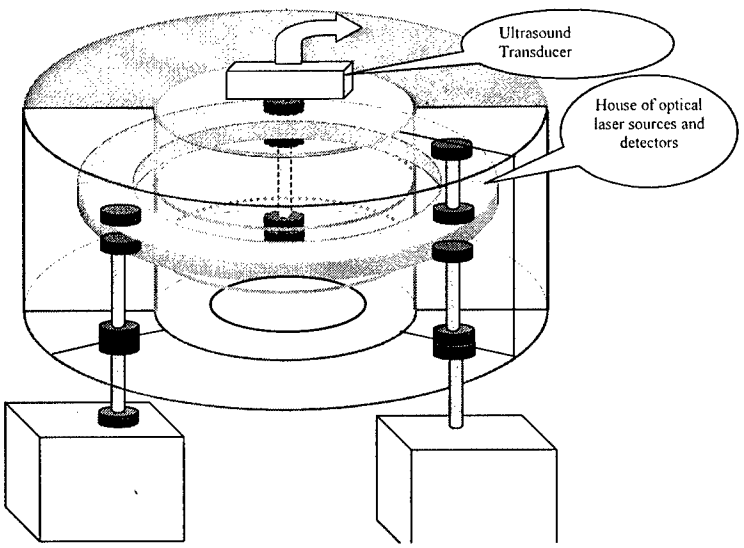
My proposed modifications are:

In the ultrasound-modulated oxygenation detection experiments, the difficulty in animal experiments was to maintain good contact between rat tumor (grew on bony flank), ultrasound transducer, and optical laser sources and detectors. Using the experimental tank that we have constructed for photo-acoustic small animal study, we can place the tumor-bearing rat in the middle of the tank filled with acoustic coupling gel. US transducer can be mounted on top of the tank to radiate the sound wave to the tumor. Optical source and detectors will be mounted on a circular ring with a curvature of approximately 90 degrees with respect to the ultrasound transducer to ensure optimal detection. The modified experimental set-up is shown in the figure below and it is expected to overcome the poor contract problem encountered previously.

In the photo-acoustic small animal research project, we use a pulsed laser source to radiate the rat tumor and detect the thermoacoustic signal changes induced by laser. The thermoacoustic signals are related to tumor absorption, which could be used to deduce tumor angionesis changes.

Since the tumor cell-line preparation and the growth of tumors in rats require assistance from the University of Connecticut animal facility, I plan to conduct both experiments when the photo-acoustic system is ready for the animal experiments. Therefore, we can efficiently use our available resources and animals. The

photo-acoustic system is currently under intensive construction and testing and we expect that it will be ready by early Jan 2006.



Proposed tasks in the original proposal

Task 1: Monitoring cancer oxygenation changes induced by ultrasound with NIR dual wavelength system (months 1 to 12)

a. Calibration and testing of the existing NIR imager for oxyHb and deoxyHb measurements.
b. Study imaging algorithms for oxyHb and deoxyHb calculation.

Task 2: Optimizing ultrasound radiation parameters toward maximizing primary radiation force (months 3 to 24)

a. Optimizing ultrasound system parameters such as pulse duration, radiation pressure, and pulse repetition frequency, toward maximizing induced oxygenation changes.
b. Instrumentation and testing of the ultrasound system.

Task 3: Conducting animal experiments with rat tumor models to assess the oxygen diffusion enhanced by ultrasound (months 4:36).

a. Animal experiments
b. Data analysis

Instrumentation improvement

References:

[1]. Pinder SE., Wencyk P., Sibbering DM., et al. Assessment of the new proliferation marker MIB1 in breast carcinoma using image analysis: associations with other prognostic factors and survival. Br J Cancer. 1995; 71:146–149.

[2] Pertschuk LP., Feldman JG., Kim YD., et al. Estrogen receptor immunocytochemistry in paraffin embedded tissues with ER1D5 predicts breast cancer endocrine response more accurately than H222Sp gamma in frozen sections or cytosol-based ligand-binding assays. Cancer. 1996; 77:2514–2519.

[3] Thor AD., Moore DHI., Edgerton SM, et al. Accumulation of p53 tumor suppressor gene protein: an independent marker of prognosis in breast cancers. J Natl Cancer Inst. 1992; 84:845–855.

[4] Sagar SM., Klassen GA., Barclay KD., Aldrich JE. Antitumor treatment: tumor blood flow—measurement and manipulation for therapeutic gain. Cancer Treat Rev. 1993; 19:299–349.

[64] Jain RK. Haemodynamic and transport barriers to the treatment of solid tumors. Int J Radiat Biol. 1991; 60:85–100.

[5] Kedar RP., Cosgrove DO., Smith IE., Mansi JL., Bamber JC. Breast carcinoma: measurement of tumor response to primary medical therapy with color flow Doppler imaging. Radiology. 1994; 190:825–830.
[6] Vaupel P., Schlenger K., Knoop C., Hockel M. (1991). Oxygenation of human tumors: evaluation of tissue oxygen distribution in breast cancers by computerized O2 tension measurements. Cancer Research, 51:3316-3322.
[7] Teicher BA. Hypoxia and drug resistance. Cancer Metastasis Rev. 1994; 13:139–168.
[8] Willett C., Boucher Y., Tomaso E et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer, Nature Medicine, Vol 10 (2), February 2004.